

PATENT SPECIFICATION

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COMPLETE SPECIFICATION

Deuteration

I, NGUYEN DINH-NGUYEN, and I, EINAR AUGUST STENHAGEN, a citizen of Viet-Nam and a citizen of Sweden, respectively, and of Hagäkersgatan 30A, Mölndal, Sweden, and Inriggaregatan 7, Mölndal, Sweden, respectively, hereby declare the invention for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention relates to a novel method of deutrating hydrogen-containing organic compounds.

Various methods for synthesising organic compounds having heavy isotopes of hydrogen chemically bonded thereto have been described previously. Generally these methods have only allowed a complete replacement of hydrogen by deuterium in low molecular weight compounds, and complete replacement in high molecular weight compounds has not been achieved. For example, hydrogen-containing organic compounds have been treated with heavy water in the presence of an alkali and a platinum catalyst. This allows the replacement of particularly labile hydrogen atoms but does not constitute a general method for the complete exchange of all the hydrogen atoms in high molecular weight compounds.

The present invention provides a general process for the complete replacement of light hydrogen by deuterium in hydrogen-containing organic compounds, including compounds of high molecular weight. According to the present invention this can be achieved by using an additional catalyst (hereinafter referred to as the promoter).

Accordingly the present invention provides a process of producing deuterated organic compounds which comprises deutrating the corresponding hydrogen-containing organic compound with deuterium oxide in the presence of an alkaline deuteroxide, as hereinafter defined, a metal catalyst of the platinum group and a deuterium peroxide promoter.

[Price 4s. 6d.]

The new process can be used not only for the small scale production of deuterated organic compounds for scientific purposes but also on an industrial scale.

Hydrogen-containing organic compounds which may be deuterated according to the present invention include hydrogen-containing fatty acids, dicarboxylic acids, ketones, alcohols and hydrocarbons. The process can be used for the preparation of deuterium-containing compounds of high isotopic purity (over 99 percent), the purity being limited only by the isotopic purity of deuterium source.

Among the catalysts which may be used in the process of the present invention the reduced form of Adams platinum oxide catalyst has been found very suitable. This catalyst, which may be obtained by the reduction of



in suspension in deuterium oxide with deuterium gas has a high activity.

The alkaline-deuteroxide, which may be defined as any alkali metal or alkaline earth metal deuteroxide provided the metal does not form insoluble products with the hydrogen-containing organic compound, and deuterium peroxide promoter can be prepared together by reacting the peroxide of an alkali or alkaline earth metal with deuterium oxide. The use of granulated sodium peroxide is preferred. It is preferred that the amounts of sodium peroxide are adjusted so that the sodium deuteroxide (i.e. the alkaline catalyst) and deuterium peroxide (i.e. the promoter) are formed in equivalent amounts, but differing amounts of basic catalyst and promoter can be used.

Suitably, the starting material is heated in a solution of an alkaline-deuteroxide in deuterium oxide in the presence of deuterium peroxide and the metal catalyst in a closed vessel with continuous shaking. The deuterated compounds are isolated from the reaction mix-

ture by conventional methods. The metal catalyst can be recovered and reconverted to its initial active form. The alkali or alkaline earth metal which results can also be recovered, if required. Several factors are of importance in influencing the extent of exchange in a single run, and such factors include the temperature, the relative amount of catalyst, and the time of heating. The optimum conditions can be found by routine experiment. The nature of the metallic catalyst and the structure of the organic compound, of course, also influence the extent of the deuteration. It is important to avoid isotope dilution.

In the laboratory heavy-walled reaction tubes of a resistant glass, such as "Pyrex" (Registered Trade Mark), can be used, but the tubes should be used only once. Preparation on a larger scale requires heated high-pressure vessels with inert inner surfaces. In the former cases the tubes are placed in an effective shaking machine in a thermostat controlled oven, and in the latter suitable means for effective stirring of the contents of the reaction vessel must be provided.

The following Examples illustrate the invention. Parts are by weight unless otherwise stated.

EXAMPLE 1

Perdeutero-octadecanoic Acid

Preparation of the metal catalyst

24.5 Parts of Adams catalyst ($\text{PtO}_2 \cdot \text{H}_2\text{O}$) and 100 parts of heavy water (99.78% D_2O from Norsk Hydro) are introduced into a reaction vessel. After evacuating the air deuterium gas is admitted, and the vessel is shaken until the platinum oxide has been completely reduced.

Preparation of alkaline catalyst and promoter

15.5 Parts of granular sodium peroxide (Na_2O_2 pro analysis from E. Merck AG), are added cautiously, in small portions, to 1000 parts of heavy water, with cooling. The resulting solution contains theoretically 16.4 parts of sodium deuterioxide and 7.2 parts of deuterium peroxide (alkaline catalyst and promoter respectively).

The exchange reaction

After introducing successively 57 parts of *n*-octadecanoic (stearic) acid, the solution of alkaline catalyst and promoter, and 400 parts of heavy water into the reaction vessel, the system is frozen in dry-ice, air is removed by evacuation and the vessel hermetically sealed.

The system is heated to 240° , and kept at this temperature for 28 hours with vigorous shaking. After cooling, the vessel is unsealed, and the resulting heterogeneous mixture is stirred until homogeneous. The water (a mixture of H_2O , HDO and D_2O) is evaporated *in vacuo* at room temperature.

1500 Parts of heavy water are added to the dry powdered residue in the reaction vessel, and the vessel is sealed after evacuation. This second exchange reaction is executed under the same conditions as that of the first one just described. After evaporating to dryness and acidifying with dilute hydrochloric acid, the organic phase is extracted with ether. The crude product chromatographed on a silicic acid column.

57 Parts (90 percent of the theoretical amount) of perdeutero-octadecanoic acid are obtained. Mass spectrometric analysis of the methyl ester showed that the acid had an isotope purity of >98%.

The synthesis can be summarised as follows.

Compounds	Molecular Weight	Molecular Ratios	Parts by weight
$\text{CH}_3-(\text{CH}_2)_{16}-\text{COOH}$	284.468	2	57
D_2O	20.028	1500	3000
$\text{PtO}_2 \cdot \text{H}_2\text{O}^*$	245.246	1	24.5
Pt	195.09	1	(19.5)
Na_2O_2^*	77.994	2	15.5
NaOD	41.011	4	(16.4)
D_2O_2	36.028	2	(7.2)
$\text{CD}_3-(\text{CD}_2)_{16}-\text{COOH}$	319.678	2	(63.8)57

80 The total reaction time is 56 hours. The starting material for the catalysts and promoter are marked with an asterisk. The figures within brackets are theoretical values.

EXAMPLE 2

Perdeutero-camphor

- Camphor contains three methyl groups whose hydrogen atoms are difficult to exchange. In order to show the efficiency of the present process in a difficult case only one hydrogen-deuterium exchange was made. In the present case, the reaction product was extracted with anhydrous ether from the reaction mixture.

From 60.8 parts of camphor the process yields

62 parts of deuterated product, no by-products being detected by gas-chromatographic analysis. Mass-spectrometric analysis of this isoprenoid compound showed the presence of some $C_{15}H_{14}O$, but the principal compound was $C_{15}H_{12}D_{12}O$. The overall exchange in this single run was about 78 percent, calculated from the mass spectrum.

The synthesis is summarised in the following Table.

Compounds	Molecular Weight	Molecular Ratios	Parts by weight
$C_{10}H_{18}O$	152.228	4	60.8
D_2O	20.028	1000	2000
$PtO_2 \cdot H_2O^*$	245.246	1	24.5
Pt	195.09	1	(19.5)
$Na_2O_2^*$	77.994	2	15.5
NaOD	41.011	4	(16.4)
D_2O_2	36.028	2	(7.2)
$C_{10}D_{18}O$ + analogues with lower deuterium content	168.324	4	(67.2)62

EXAMPLE 3

Perdeuteroanthracene

- The synthesis was performed under the same conditions as used for the preceding compounds. The hydrogen atoms in anthracene are easy to exchange and a single run gives a fully deuterated product. Separation of the expected compound from the resulting mixture was performed (after evaporating off water (H_2O, HDO, D_2O)) by extraction with dry

benzene. The light yellow extract was then concentrated by evaporation at room temperature, and heptane was added to precipitate the final deuterated polycyclic hydrocarbon, 53.4 Parts of anthracene thus yielded 48 parts (85 percent) of perdeuteroanthracene of high isotopic purity, as shown by mass spectrometric analysis (>99 percent).

The synthesis is summarised in the following Table:

Compounds	Molecular Weight	Molecular Ratios	Parts by weight
$C_{14}H_{10}$	178.220	3	53.4
D_2O	20.028	1000	2000
$PtO_2 \cdot H_2O^*$	245.246	1	24.5
Pt	195.09	1	(19.5)
$Na_2O_2^*$	77.994	2	15.5
NaOD	41.011	4	(16.4)
D_2O_2	36.028	2	(7.2)
$C_{14}D_{10}$	188.280	3	(56.4)48

WHAT WE CLAIM IS:—

1. A process of producing deuterated organic compounds which comprises deuterating the corresponding hydrogen-containing organic compound with deuterium oxide in the presence of an alkaline deuterioxide, as hereinbefore defined, a metal catalyst of the platinum group and a deuterium peroxide promoter.
2. A process according to claim 1, wherein the alkaline deuterioxide and promoter are prepared jointly by reacting an alkali metal or alkaline earth metal peroxide with a deuterium oxide.
3. A process according to claim 1 or 2, wherein the metal catalyst is prepared by reducing a suspension of Adam's platinum oxide catalyst in deuterium oxide with deuterium gas.
4. A process according to any one of the preceding claims, in which the organic compound is a hydrogen-containing fatty acid, dicarboxylic acid, ketone, alcohol or hydrocarbon.
5. A process according to any one of the preceding claims, in which the deuteration is carried out in a closed vessel under conditions of vigorous shaking, and at an elevated temperature.
6. A process of producing deuterated organic compounds according to claim 1, substantially as hereinbefore described.
7. A process of producing deuterated organic compounds substantially as described in any one of Examples 1 to 3.
8. Deuterated organic compounds whenever produced by a process as claimed in any one of claims 1 to 7.

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